REMARKS

The title has been amended to conform to the nature of the claimed subject matter. Claims 43 and 44 were amended to delete inadvertent inclusion of the canine brain natriuretic peptide as claims to the detection of the human peptide have been elected. There is only one basis for rejection based on § 103.

The Rejection Under 35 U.S.C. § 103

Claims 32 and 41-44 were rejected as obvious over Sudoh, *et al.* in view of Hirth, *et al.* Claim 32 is drawn to antibodies useful for immunoassays to detect a peptide, which comprises human brain natriuretic peptide of the formula: Ser-Pro-Lys-Met-Val-Gln-Gly-Ser-Gly-Cys-Phe-Gly-Arg-Lys-Met-Asp-Arg-Ile-Ser-Ser-Ser-Ser-Gly-Leu-Gly-Cys-Lys-Val-Leu-Arg-Arg-His, or a C-terminal amide thereof. Claims 41-44 are drawn to the antibodies of claim 32 wherein the antibodies are monoclonal, to the antibodies further comprising a label, to methods to perform immunoassays using these antibodies, and to a kit for conducting these immunoassays.

The Cited Art.

Hirth teaches methods to produce antibodies against atrial natriuretic peptide (ANP). It provides methods to prepare monoclonal antibodies to both rat ANP (rANP) and human ANP (hANP), using the known sequence of these peptides. The method of Hirth teaches use of hANP to produce antibodies suitable to detect hANP, but it does not teach, for example, that the rat peptide, rANP, could be used to prepare antibodies useful to detect hANP, or vice versa.

Sudoh discloses the isolation of a new peptide from porcine brain: this peptide is referred to as brain natriuretic peptide (BNP), and is homologous to ANP. Sudoh also discloses the sequence of the 26-residue polypeptide that comprises porcine BNP (pBNP) and speculates that BNP may be present in other mammals and involved in homeostatic regulation. However, Sudoh does not disclose the existence or structure of the human peptide, hBNP.

The Office implies that one of ordinary skill would have found it obvious to use the porcine protein taught by Sudoh to generate antibodies by the method of Hirth, and that

> absent evidence to the contrary, one having ordinary skill in the art would have expected at the time of filing that antibodies targeting porcine BNP would share some sequence homology to human BNP and would likely have cross reactivity with human BNP.

Office Action mailed 3/25/2003, page 4. Applicants respectfully assert that this actually not the case and that the disclosure of Sudoh demonstrates that there would not be cross-reactivity of antibodies raised against porcine BNP with any human counterpart. For this and other reasons, applicants believe this rejection should be withdrawn.

Argument.

Applicants respectfully submit that the Office has not established a *prima facie* case of obviousness in this instance for at least three reasons. First, the cited art does not teach even the existence of human BNP, whose existence is a necessary prerequisite for the antibodies of the claimed invention. Second, the cited art does not provide motivation to combine the teachings of Hirth and Sudoh, because Sudoh not only discloses a method for detecting BNP without using antibodies, but shows that antibodies raised against ANP do not cross react with pBNP. Finally, the cited art does not provide a reasonable expectation of success for producing antibodies against hBNP, because it provides no evidence that antibodies against hBNP could be prepared without knowing the sequence of hBNP, *i.e.*, Sudoh discloses evidence that would lead one of ordinary skill to expect that antibodies against pBNP would not detect hBNP.

The cited art does not teach the existence of human BNP.

Sudoh discloses the existence and the amino acid sequence of pBNP, and as the Office observed, it also "speculates that it is probable that BNP is present in other organs, such as heart, wherein it may function in concert with ANP..." Applicants concede that Sudoh thus provides motivation for further research into the function of pBNP in pigs and a search for corresponding peptides in other animals. However, Sudoh does not demonstrate that BNP is present in other organs in the pig, let alone in mammals in general or in humans in particular. While one of ordinary skill would probably be motivated to research the presence of BNPs in other mammals,

Sudoh only presumes that such proteins exist. The prior art does not disclose the existence of any other BNP peptides besides pBNP, so even the existence of this peptide is speculative.

The prior art does not provide motivation to combine the teachings of Hirth and Sudoh.

Sudoh not only discloses the isolation and investigation of pBNP without using any antibodies, Sudoh also discloses that antibodies raised against ANP do not cross react with pBNP. While Sudoh discusses "ANP-like" immunoreactivity that was observed during the purification process, a careful reading shows that the ANP-like immunoreactivity was not associated with BNP, "*ANP-like immunoreactivity emerged in fraction C", while pBNP was isolated from fraction B.* (Sudoh, pg. 79, legend for Figures 1a and 1b.) Rather, ANP-like activity detected by the ANP antibody led to isolation of two truncated ANP derivatives from fraction C. The novel peptide, pBNP, was isolated by further fractionation of fraction B, using the relaxant assay to guide successive chromatographic separations *because the immunoassay did not detect pBNP.*

From Sudoh, one of ordinary skill would learn that hANP antibodies do not detect pBNP, and that the relaxant assay detects pBNP sufficiently well to guide fractionation. Thus Sudoh provides motivation for continued study of BNP peptides using the relaxant assay, and does not suggest that antibodies are necessary or advantageous for any reason.

The prior art does not provide a reasonable expectation of success.

A rejection for obviousness requires a "reasonable expectation of success." *In re Vaeck* 947 F2d 488,493 (Fed. Cir. 1991). The Office assumes, without evidence, that one of ordinary skill would expect the BNP polypeptide to be present in other species and to be highly conserved across species. Sudoh provides evidence to contradict this: comparison of the rat and human ANP peptides shows that species differences occur and that they are immunologically significant, even where the difference is a single residue.

The information in Sudoh indicates that the combination proposed by the Office would only work if the 17-residue sequence defined by the pair of cysteine residues is almost completely conserved across species. While the Office notes that "some sequence homology" between pBNP and hBNP would be expected, Sudoh demonstrates that antibody crossreactivity

requires substantial sequence identity rather than "some homology". The prior art does not disclose the existence of BNPs in other species, nor any evidence that BNP sequences are highly conserved across species; instead, it provides evidence that the related ANP sequences differ across species in a critical 17-residue segment, and that high crossreactivity is not expected if any variation occurs in this segment. Therefore, the cited art does not provide a reasonable expectation of success for production of antibodies against hBNP by using the sequence of pBNP in the methods of Hirth. A reasonable expectation of success is required as "obvious to try" is not a proper basis for an obviousness rejection. In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

The disclosure of Sudoh would lend the artisan to expect failure, even if the combination suggested by the Office were suggested by the art. And this failure is confirmed by examining the structures of pBNP and hBNP. In Sudoh, the relaxant assay was used during the purification of pBNP by Sudoh because, as Figure 1a shows, the anti-ANP immunoassay did not detect pBNP, even though ANP and BNP are described as showing "remarkable homology". Sudoh, page 80, first paragraph. Yet, despite this "remarkable homology", there was no cross-reactivity of pBNP with the anti-ANP antibody. According to Sudoh,

> The 17 amino-acid sequence (a-ANP[7-23]) flanked by two Cys residues, thought to be essential for ANP activity, is highly conserved in the molecule of pBNP, although four residues in this region are replaced. This may explain the fact that **pBNP does not crossreact with anti-a-hANP antibody, which is only 20% crossreactive even with rat a-ANP** (a-rANP), which has only a single replacement (Met-to-Ile) at position 12...

Id., emphasis added. Thus changing a single amino acid in the 17-residue sequence defined by the two cysteine residues reduced crossreactivity five-fold, and changing four such amino acid residues eradicated crossreactivity altogether.

Looking at the 17-residue sequence defined by the two cysteine residues, the sequence of hBNP disclosed in the application includes four residues that differ from the pBNP sequence disclosed in Sudoh. The relevant 17-residue segments are presented here, with the residues that differ between pBNP and hBNP highlighted for clarity:

pBNP: Cys-Phe-Gly-Arg-**Arg**-**Leu**-Asp-Arg-Ile-**Gly**-Ser-**Leu**-Ser-Gly-Leu-Gly-Cys

hBNP: Cys-Phe-Gly-Arg-**Lys**-**Met**-Asp-Arg-Ile-**Ser**-Ser-**Ser**-Ser-Gly-Leu-Gly-Cys

Based on this substantial difference between the sequences, the teachings of Sudoh suggest that antibodies to pBNP should not crossreact with hBNP; the sequence differences are too substantial. In fact, in the 17-residue segment that Sudoh describes as "highly conserved", the difference between hBNP and pBNP, four amino acid substitutions, is the same as the difference between hANP and pBNP, where crossreactivity was absent. Thus, even if the Office had established a *prima facie* case for obviousness, this evidence demonstrates that the proposed combination of the teachings of Sudoh and Hirth probably would not produce an anti-hBNP antibody.

This rebuts any asserted *prima facie* case for obviousness: In re Papesch (315 F.2d 381, 386-87 (CCPA 1963)) says, "If that which appears, at first blush, to be obvious though new is shown by evidence not to be obvious, then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall." Here, even if the combination could have appeared obvious prior to the Applicant's determination of the sequence of hBNP, after that sequence was determined, one of ordinary skill in the art would recognize that the pBNP sequence probably could not be used to generate anti-hBNP antibodies.

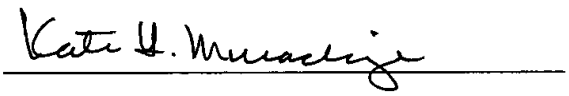
CONCLUSION

Applicants have demonstrated that the cited art does not support a key assumption underlying the Office's *prima facie* case for obviousness. Also, applicants have shown that the prior art discloses a bioassay useful for further study of BNPs without using antibodies, and never suggests the preparation of antibodies to BNP's in general or to hBNP in particular. Applicants have further demonstrated that the combination proposed by the Office, even if obvious to try, could not have a reasonable expectation of success. The prior art suggests that antibodies to detect hBNP could not be generated using pBNP. Accordingly, the rejection of the pending claims as obvious over Sudoh in view of Hirth should be withdrawn.

Thus, it is believed that claims 32 and 41-44 are in condition for allowance. Reconsideration and allowance of these claims is respectfully requested in light of the foregoing discussion.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 219002025213.

Respectfully submitted,

Dated: July 24, 2003 By: 

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